IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM Plaintiff, vs. ALNYLAM PHARMACEUTICALS INC. AND ALNYLAM U.S., INC. Defendants	Civil Action No. 1:24-cv-1524-DAE JURY TRIAL DEMANDED

DEFENDANTS' ANSWER TO COMPLAINT AND AFFIRMATIVE DEFENSES

Defendants Alnylam Pharmaceuticals Inc. and Alnylam U.S., Inc. ("Alnylam") by their undersigned attorneys, hereby file their answer and affirmative defenses ("Answer") to the Complaint filed by The Board of Regents of the University of Texas System ("The Board" or "Plaintiff"). Each of the paragraphs below corresponds to the same numbered paragraphs in the Complaint. In responding to the Complaint, Alnylam has kept Plaintiff's headings for ease of reference, but in doing so, Alnylam is not admitting to the accuracy of any statements made or agreeing with any characterizations made in such headings. Alnylam denies all allegations in the Complaint, whether express or implied, that are not specifically admitted below. Alnylam further denies that Plaintiff is entitled to the relief requested in the Complaint, or to any other relief.

THE NATURE OF THE ACTION

1. Alnylam denies the allegations in Paragraph 1, except that Alnylam admits that The University of Texas M.D. Anderson Cancer Center is a member institution of The University of Texas System.

2. Alnylam is without knowledge or information sufficient to form a belief as to the truth of the allegations in Paragraph 2 and therefore denies them. The '717 Patent speaks for itself.

3. Alnylam denies the allegations in Paragraph 3, except it admits that between 2007 and 2009 Alnylam and representatives of Plaintiff met and/or corresponded regarding alleged approaches and/or technology being developed by representatives of Plaintiff.

4. Alnylam denies the allegations in Paragraph 4 except it admits that it had no commercial product as of 2007. Alnylam also admits (i) that in its 2016 Form 10K, Alnylam stated that as of December 31, 2016, it had an accumulated deficit of $1.66 billion, and (ii) that its first commercial product, Patisiran, sold under the brand name ONPATTRO®, and was approved by the U.S. Food and Drug Administration in 2018.

5. Alnylam denies the allegations in Paragraph 5, except it admits that ONPATTRO® treats a rare and, if untreated, fatal genetic disease known as polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN). Alnylam admits that ONPATTRO® works by delivering siRNA into the patient's cells.

6. Alnylam denies the allegations in Paragraph 6 except it admits that for some period of time ONPATTRO® was the only FDA-approved treatment for hATTR-PN and Alnylam's only commercial product, that its worldwide revenue for sales of ONPATTRO to date exceed $1.3 billion, and that hATTR-PN amyloidosis patients were at risk of death without ONPATTRO® treatment.

7. Alnylam denies the allegations of Paragraph 7, except it admits that there is no license agreement between Plaintiff and Alnylam to the '717 Patent.

THE PARTIES AND JOINDER

8. Alnylam is without knowledge or information sufficient to form a belief as to the truth of the allegations in Paragraph 8 and therefore denies them.

9. Alnylam denies the allegations in Paragraph 9 except that it admits that Alnylam Pharmaceuticals Inc. is a corporation organized and existing under the laws of Delaware.

10. Paragraph 10 contains legal conclusions to which no response is required. Alnylam denies the allegations in Paragraph 10 except it admits that Alnylam U.S. Inc. is a corporation organized and existing under the laws of Delaware and is a wholly owned subsidiary of Alnylam Pharmaceuticals Inc.

SUBJECT MATTER JURISDICTION

11. Admitted.

PERSONAL JURISDICTION AND VENUE

12. Alnylam denies the allegations in Paragraph 12.

13. Alnylam denies the allegations in Paragraph 13.

14. Alnylam denies the allegations in Paragraph 14.

THE '717 PATENT

15. Alnylam denies the allegations in Paragraph 15 except in so far as the '717 Patent speaks for itself.

16. Alnylam denies the allegations in Paragraph 16 and to the extent Paragraph 16 contains legal conclusions, no response is required.

17. Alnylam denies the allegations in Paragraph 17 except it admits that there is no license agreement between Plaintiff and Alnylam.

18. Alnylam denies the allegations in Paragraph 18.

COUNT I: (ALLEGED) INFRINGEMENT OF THE '717 PATENT

19. Alnylam incorporates by reference the forgoing Paragraphs.

20. Alnylam denies the allegations in Paragraph 20.

21. Alnylam denies the allegations in Paragraph 21.

22. Alnylam denies the allegations in Paragraph 22.

23. Alnylam denies the allegations in Paragraph 23.

24. Alnylam denies the allegations in Paragraph 24.

25. Alnylam denies the allegations in Paragraph 25.

26. Alnylam denies the allegations in Paragraph 26.

DEMAND FOR JURY TRIAL

27. Alnylam does not object to a trial by jury on all issues so triable.

[PLAINTIFF'S] PRAYER FOR RELIEF

Alnylam denies that Plaintiff is entitled to any relief from Alnylam, including the relief Plaintiff seeks in its Prayer for Relief, Paragraphs A-G. Plaintiff's Prayer for Relief should be denied in its entirety and with prejudice, and Plaintiff should be awarded nothing. Alnylam further denies each and every allegation in Plaintiff's Prayer for Relief.

AFFIRMATIVE DEFENSES

Pursuant to Federal Rule of Civil Procedure 8(c), and without altering any applicable burdens of proof, Alnylam asserts the following defenses to the Complaint and reserves its right to assert additional defenses.

FIRST DEFENSE - NON-INFRINGEMENT

Alnylam does not infringe, has not infringed, and will not infringe directly or indirectly, any valid claim of the '717 Patent.

SECOND DEFENSE - INVALIDITY

One or more claims of the asserted '717 Patent are invalid for failure to satisfy the conditions of patentability in 35 U.S.C. §§ 101 et seq., including, but not limited to §§ 101, 102, 103, and/or 112.

THIRD DEFENSE - INEQUITABLE CONDUCT

One or more claims of the asserted '717 Patent are unenforceable for inequitable conduct during the prosecution of the '717 Patent due to failure to satisfy 37 C.F.R. § 1.56.

1. The '717 Patent is unenforceable by virtue of the doctrine of inequitable conduct before the United States Patent and Trademark Office ("USPTO").

2. Inequitable conduct occurs when a patent applicant or applicant's representative breaches their duty of candor and good faith by either misrepresenting or failing to disclose material information to the USPTO. 37 CFR § 1.56 ("Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section.") *See also Cabin Foods, LLC v. Rich Prods. Corp*, No. EP-11-CV-318-KC, 2012 U.S. Dist. LEXIS 16386 at *7 (W.D. Tex., Feb. 8, 2012).

3. 37 C.F.R. § 1.56 provides that each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the PTO, which includes a duty to disclose to the PTO all information known to that individual to be material to patentability. 37 C.F.R. § 1.56(a). Information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and it establishes, by itself or in combination with other information, a *prima facie* case of unpatentability of a claim. *Id*. at § 1.56(b)(1).

4. Pre-AIA 35 U.S.C. § 103(a), which is applicable to the '717 Patent, provides that "a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." The invention must not have been obvious to a "person having ordinary skill in the art" in view of the appropriate prior art. 35 U.S.C. § 103(a).

Inequitable Conduct

5. Plaintiff filed U.S. Patent Application No. 11/911,639 (the "'639 Application") on August 12, 2008. The '639 Application claims priority to Provisional Application No. 60/671,641 filed on April 15, 2005.

6. During the course of prosecuting the '639 Application, Plaintiff made repeated, exaggerated claims that the alleged inventors' use of a neutral liposome to encapsulate negatively charged nucleotides was novel and unexpected. Applicants referred to "the central dogma regarding the use of cationic lipids to deliver siRNA," and asserted that their discovery was "surprising and unexpected." Ex. A at 9; *See also id*. at 11 and 16; Ex. B at 16:3-5, 16:22-25; 18:3-

7; Ex. C at 7, 9 (stating that the encapsulation by a neutral liposome is "clearly a surprising and unexpected result!").

7. Plaintiff repeatedly emphasized this supposedly novel aspect of the invention in the specification as well, stating that "the inventors have discovered that non-charged liposomes may be efficiently used to deliver an inhibitory nucleic acid such as siNA or siRNA," and falsely alleging that prior work taught away from the idea that neutral liposomes would be effective. '717 Patent at 2:1-10 and 19-21, *see also* 9:41-43.

8. In support of the '639 Application Plaintiff filed a Declaration signed by Dr. Gabriel Lopez-Berestein (the "Declaration," attached as Exhibit D), one of the named inventors of the '639 Application. The Declaration was submitted on November 9, 2010.

9. The Declaration was submitted in response to a rejection by the examiner dated September 3, 2010, wherein the examiner found that the invention was obvious in light of two prior art references: Harvie et al. (US 2003/0203865) and Hitoshi et al. (US 2004/0126784). The examiner determined that "it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Harvie et al. taken with Hitoshi, namely to produce the composition comprising a lipid component and siRNA targeting FAK." Ex. J at 8.

10. The examiner also found that the invention was obvious over Gutierrez-Puente et al. (J. Pharmacol. Exp. Thera. 291:865-9, 1999) and Hitoshi. The examiner found that "it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of the Guiterrez-Puente et al. taken with Hitoshi, namely to produce the composition comprising a lipid component and siRNA targeting FAK." *Id*. at 11.

11. Plaintiff's response advanced the Declaration to argue that "one of skill in the art at the time of the present invention" would understand "that in the case of siRNA, a cationic liposome should be employed, hence teaching away from the present invention." Ex. G at 9. Plaintiff also pointed to studies cited in the Declaration to support Secondary Considerations of Non-Obviousness. *Id*. at 10-15.

12. The Declaration summarized and presented studies to demonstrate that "the general understanding in the liposome field at a time just prior to the filing of our application was a cationic liposome was required to deliver nucleic acids, including siRNAs." Ex. D at ⁋ 2(c).

13. To this end, Dr. Lopez-Berestein cited a 1997 publication which he co-authored with Ana M. Tari, titled "Oligonucleotide Therapy for Hematological Malignancies" (hereinafter "the Publication") and published in the Journal of Liposome Research. Ex. D at ⁋ 5.

14. In his Declaration, Dr. Lopez-Berestein described the Publication as demonstrating that antisense molecules with a negatively charged backbone have a lower incorporation efficiency into neutral or negatively charged liposomes than antisense nucleotides with an uncharged backbone. *Id*. at ¶5.

15. The Declaration also discusses other articles to suggest that a person of skill would use a positively charged liposome (rather than a neutral one) to encapsulate negatively charged nucleic acids (such as siRNA or unmodified antisense oligonucleotides). *Id*. at ⁋ 6-10.

16. The Declaration relied on these articles to support the argument that "the general understanding in the literature prior to our application, in direct contrast to our invention, was that in the case of siRNA, the use of a positively charged lipid was critical." *Id*. at ¶ 11. The Declaration also argued that "in the case of siRNA our data shows that a negatively charged backbone and a neutral liposome is needed to obtain a 90% encapsulation efficiency," thereby suggesting that the

claimed neutral liposome was the reason for the better performance than the prior art cationic liposomes.

17. The Declaration was submitted to the USPTO in support of the non-obviousness of the invention, during the prosecution of the '639 Application, with Plaintiff reiterating that "the general understanding in the literature prior to our application, in direct contrast to our invention, was that in the case of siRNA, the use of a positively charged lipid was critical." *See* Ex. G at 15.

18. Dr. Lopez Berestein made these statements, despite knowing that they were contradicted by his own earlier work. Dr. Lopez-Berestein did not disclose to the Patent Office during prosecution of the '639 Application that he had sought patent protection for work 10 years earlier using a neutral liposome to encapsulate negatively charged nucleotides.

19. More specifically, Dr. Lopez-Berestein and Ana M. Tari are listed as authors on a 1997 publication under the Patent Cooperation Treaty ("PCT") titled "Liposomal Phosphodiester, Phosphorothioate, and p-Ethoxy Oligonucleotides," International Publication Number WO 97/07784 (hereinafter "PCT Publication"). This PCT Publication has an international publication date of March 6, 1997, well before Dr. Lopez-Berestein submitted his Declaration to the PTO. Ex. E. The PCT Publication claims priority to U.S. Provisional Application 08/520,385, filed on August 29, 1995. Dr. Lopez-Berestein signed a declaration on December 7, 1995, stating that the provisional application was filed on August 29, 1995, and that he had "reviewed and understand the contents of the above identified specification, including the claims." Ex. F, at 31-32.

20. The PCT Publication describes the delivery of antisense oligonucleotides using a liposome consisting of essentially neutral phospholipids. The PCT Publication describes the use of phosphodiester antisense oligonucleotides, phosphorothioate oligonucleotides, and p-ethoxy oligonucleotides. Of these varieties, phosphodiester and phosphorothioate oligonucleotides are

negatively charged, while p-ethoxy oligonucleotides are uncharged. Ex. E at 2:3-22.

21. The PCT Publication lists the preferred molar ratios for encapsulating different types of antisense oligonucleotides in neutral phospholipids, stating that,

> The composition includes (a) liposome which consists essentially of neutral phospholipids, and (b) an antisense oligonucleotide…When the antisense oligonucleotide is a phosphodiester oligonucleotide, the preferred molar ratio of phospholipid to oligo is less than about 3,000:1. When the antisense oligonucleotide is a phosphorothioate oligonucleotide, the preferred molar ratio of phospholipid to oligo is about 10:1 and about 50:1. When the antisense oligonucleotide is a p-ethoxy oligonucleotide, the preferred molar ratio of phospholipid to oligo is between about 5:1 and about 100:1.

Ex. E at 2:26-3:10.

22. The PCT Publication makes it clear that negatively charged oligonucleotides such as phosphorothioate can be encapsulated in neutral liposomes by varying the molar ratio of phospholipid to oligonucleotide. Specifically, the PCT Publication at 10:7-14 set forth the following data:

> Development of liposomal-phosphorothioates
>
> Similar incorporation protocol was used with phosphorothioates (PT) since PT and PD are structural analogs. Various molar ratios of DOPC to PT were used (Table 4). The effect of sonication of the liposomal mixture (before dialysis) was also studied.
>
> Table 4
>
> Effect of lipid to oligonucleotide molar ratios on the incorporation of PT into liposomes.

Molar ratio	% incorporation without sonication	with sonication
10/1	>90	>90
50/1	>90	>90
100/1	45.8	55.5
200/1	44.1	49.1
500/1	27.8	47.0
1000/1	25.1	42.1

23. Dr. Lopez-Berestein was aware of the PCT Publication and/or its contents as of at least 1997 because he is listed as an inventor on the PCT Publication and signed a declaration to that effect. Ex. E; Ex. F, at 31-32.

24. Since Dr. Lopez-Berenstein was aware that negatively charged oligonucleotides could be encapsulated in neutral liposomes as of 1997, his statements in his Declaration submitted to the USPTO in 2010 that a person of skill in the art prior to the publication of the '639 Application would only have considered cationic liposomes for the encapsulation of siRNA (a negatively charged oligonucleotide) in 2007 constitute a knowing misrepresentation. The single most reasonable inference to be drawn from these facts is that Dr. Lopez-Berenstein's conduct was the result of a specific intent to deceive USPTO.

25. Dr. Lopez-Berenstein's misrepresentation(s) constituted a breach of his duty of good faith and candor under 37 CFR § 1.56.

26. Dr. Lopez-Berenstein's consistent misrepresentations, in both his Declaration and throughout the specification, and their persistent citation by applicants, including Dr. Lopez-Berenstein, in support of the '639 Application over the obviousness rejection (along with his concealment of the PCT Publication and its contents) were material under the "but for" materiality standard to the PTO's decision to ultimately issue the '639 Application as US Patent No. 8.895,717. *See* Ex. G at 15; Ex. H at 8, 10; Ex. I at 10-13. *See also* '717 Patent at 2:1-10; 2:19-21; 9:41-43.

Egregious Misconduct

27. Alternatively, inequitable conduct can also be shown by proving the patentee engaged in affirmative acts of egregious misconduct. Courts have held that, "[w]hen the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably

false affidavit, the misconduct is material. . .. After all, a patentee is unlikely to go to great lengths to deceive the PTO with a falsehood unless it believes that the falsehood will affect issuance of the patent." *Therasense, Inc. v. Becton, Dickinson & Co*., 649 F.3d 1276, 1292 (Fed. Cir. 2011) (citing *See Rohm & Haas Co. v. Crystal Chem. Co*., 722 F.2d 1556, 1571 (Fed. Cir. 1983) ("there is no room to argue that submission of false affidavits is not material"); *see also Refac Int'l, Ltd. v. Lotus Dev. Corp*., 81 F.3d 1576, 1583 (Fed. Cir. 1996) (finding the intentional omission of declarant's employment with inventor's company rendered the affidavit false and that "[a]ffidavits are inherently material")).

28. In view of the PCT Publication discussed above and/or its contents, the Declaration is clearly a "false affidavit." The Declaration contained knowingly false information about the status of the prior art and Dr. Lopez-Berestein's own published work without bringing to the Patent Office's attention the PCT Publication and/or its contents as discussed above. Dr. Lopez-Berestein signed the Declaration under penalties of perjury and provided it to the USPTO, despite knowing it contained false information. Such affirmative egregious misconduct of filing an unmistakably false Declaration is per se material to the application.

29. Dr. Lopez-Berestein engaged in inequitable conduct in the specification and during the prosecution of the '717 Patent. Thus, the '717 Patent is unenforceable.

FOURTH DEFENSE- LACK OF PROPER VENUE

Venue is not proper in the Western District of Texas under 28 U.S.C. § 1400(b), because Alnylam neither resides in nor has a regular and established place of business in the Western District of Texas, as further set forth in Alnylam's Motion to Dismiss, incorporated herein. *See* Dkt. 21; 25.

FIFTH DEFENSE- UNCLEAN HANDS

The foregoing conduct described in the Third Affirmative Defense and incorporated herein constitutes unclean hands.

SIXTH DEFENSE - ADDITIONAL DEFENSES

Alnylam reserves the right to assert further defenses in the event that discovery indicates such defenses would be appropriate.

Dated: July 16, 2025

Respectfully submitted,

/s/ Samoneh Schickel

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CERTIFICATE OF SERVICE

I hereby certify that the foregoing is being served via electronic mail on July 16, 2025, on all counsel of record who consent to electronic service.

By: */s/ Samoneh Schickel*
Samoneh Schickel